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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/777,820	COLLINS ET AL.	
	Examiner	Art Unit	
	David Lukton	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-71 and 75-141* is/are pending in the application.

4a) Of the above claim(s) *70,71,79,81 and 90-141* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *69,75-78,80 and 82-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the response filed 9/12/06, claims 1-68 have been cancelled, claims 69 & 70 amended, and claims 75-141 added. Claims 69-71, 75-141 are now pending.

Claims 69, 75-78, 80, 82-89 are examined in this Office action; claims 70, 71, 79, 81, 90-141 are withdrawn from consideration.

Applicants' arguments filed 9/12/06 have been considered and found persuasive in part. The §103 rejections over each of Glass ('902), Griffin ('786) and Schinazi ('796) are withdrawn.

✦

Claim 69 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 16 of copending application Serial No. 10/028,857. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 16 of the copending application is drawn to a method for treating a "proliferative disorder". Certainly, a tumor would qualify as such a disorder. In addition, the genus of formula I of the '857 application overlaps genus of formula I of the instant application. [This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented].

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a

second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application . See 37 CFR 1.78(d).

✧

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 69, 75-78, 80, 82-89 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It may be the case that the following claim is enabled:

> *100. A method of inhibiting the binding of cyanocolablamin to a transcobalamin protein comprising contacting a compound according to claim 1 with a transcobalamin protein for a time and under conditions effective to inhibit the binding of cyanocolablamin to the transcobalamin protein.*

However, claim 69 is drawn to a method of treating cancer by administration of a compound which contains boron. For the treatment to be successful, however, localization at the site(s) of the tumor would be required. As disclosed in Yong (*Anticancer Research* **15**, 2033-38, 1995) carboranylalanine was taken up *in vitro* by

melanoma cells, but was not taken up significantly when administered *in vivo*, either by melanoma tissue, or by glioma-bearing rats. This reference supports the conclusion of "unpredictability" in extrapolating from in vitro tissue uptake results to an *in vivo* therapy.

Applicants have pointed to example 9 of Collins (USP 5,739,313; at col 11, line 35+), where data is presented on a methylcobalamin DTPA ^{111}In complex that was administered to Balb-C mice. There is no indication of where (anatomically) the tumor was implanted, but judging from Collins, D. A., (*J. Nucl. Med.* 38(5) 717-23, 1997), what may have been done is to inject ATCC CCL8 sarcoma cells into the left flank of the mice. According to the data in table III (cols 11-12 of USP '313), there was some uptake of the DTPA complex into the tumor cells. But the instant claims are not drawn to a method of achieving uptake into tumor cells. The claims require that reduction in tumor volumes be achieved, or at the very least, that the tumors stop growing. Collins (USP '313) has made no attempt to show that this is possible. Among the various questions to be answered are whether selective uptake of the claimed conjugates is exhibited by tumors in general, or whether only certain tumors will take up the claimed conjugates. Many of the following would be included:

> breast cancer, prostate cancer, lung cancer, colon cancer, rectal cancer, bladder cancer, Non-Hodgkin Lymphoma, melanomas of the skin, cancer of the Kidney and Renal Pelvis, pancreatic cancer, oral cancer, esophagal cancer, ovarian cancer, thyroid cancer, stomach cancer, brain cancer, multiple myeloma, liver and intrahepatic bile duct cancer, acute

myeloid leukemia, chronic lymphocytic leukemia, Hodgkin's Lymphoma, testicular cancer, intestinal cancer, chronic myeloid leukemia, acute lymphocytic leukemia, cancer of the vulva, gallbladder cancer, malignant mesothelioma, bone cancer, joint cancer, cancer of the hypopharynx, cancer of the eye, cancer of the nose, cancer of the ureter, cancer of the peritoneum, gastrointestinal carcinoid tumors, bladder cancer, melanoma, breast cancer, non-hodgkin's lymphoma, ovarian cancer, endometrial cancer, pancreatic cancer, kidney cancer (renal cell), prostate cancer, leukemia, non-melanoma cancer of the skin. Also included are sarcomas and carcinomas, such as the following: fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinoma, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, lymphoma, multiple myeloma, Waldenströom's macroglobulinemia, and heavy chain disease.

The following references discuss the matter of various attempts by oncologists to treat cancer: Viallet (*Lung Cancer* 15 (3) 367-73, 1996); Kemeny (*Seminars in Oncology* 21 (4 Suppl 7) 67-75, 1994); Newton (*Expert Opinion on Investigational Drugs* 9 (12) 2815-29, 2000); Giese (*Journal of Cancer Research and Clinical Oncology* 127 (4) 217-25, 2001); Garattini (*European Journal of Cancer* 37 Suppl 8 S128-47, 2001); Ragnhammar (*Acta Oncologica* 40 (2-3) 282-308, 2001). A recurring theme is that of the failure to achieve selective toxicity. Such will be the case with the claimed conjugates.

Then there is the matter of large solid tumors. What is the efficacy there?

Then there is the matter of how one goes about applying an energy source to the site(s) of

the tumors. The claims encompass subjecting the afflicted mammal to any and all forms of energy, any and all amounts of energy, and applying that energy to any and all anatomical locations. Surely not all of this is enabled. A step in the direction of overcoming this ground of rejection would be to require that thermal neutron irradiation be used and that it be targeted to the relevant anatomical sites. However, it would still remain an open question as to which forms of cancer can be successfully treated, and which anatomical locations can be accessed by the irradiation.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims.

In view of the absence of guidance, the absence of working examples, and unpredictability in the oncology field, the skilled oncologist or radiologist would conclude that "undue experimentation" would be required to practice the claimed invention.

✦

Claims 69, 75-78, 80, 82-89 are rejected under 35 U.S.C. §112 second paragraph, as being

indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 69 is indefinite as to the process steps of the "administering neutron capture therapy". What does the medical practitioner do, and what does he (or she) see? Does the neutron capture therapy require any external energy source? What is the endpoint? If the affected tissue is subjected to thermal neutron irradiation for one nanosecond, is that sufficient, in applicants' opinion to achieve a "therapy"?

In response, applicants have argued that there does exist literature on the subject of neutron capture therapy, and that the skilled artisan is free to review that literature and design his own experiments. On this particular point, there is agreement. But the issue is that of where the dividing line is between a series of steps which would qualify as a "neutron capture therapy" and a series of steps which would not. It is not clear that claim 69 requires the use of an energy source, or that, if an energy source is required, what the various options might be. For example, if a subject is suffering from pancreatic cancer, would applicants propose irradiating the brain? If a subject is suffering from breast cancer, would applicants propose irradiating the liver? It is not enough to state that others are free to design their own experiments. The issue is what the claims encompass. The following does not necessarily resolve all issues, but would at least overcome this particular ground of rejection:

A method of inhibiting growth of tumor cells present in a tissue comprising administering a compound of formula I to a mammal in need thereof, and subjecting the tissue to thermal neutron irradiation for a time and under conditions effective to inhibit growth of said tumor cells.

✦

The following is a quotation of 35 USC. §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 69, 75-79, 82-86, 89 are rejected under 35 U.S.C. §103 as being unpatentable over Collins (USP 6,004,533) in view of Schinazi (USP 5,599,796).

As indicated previously, Collins discloses compounds in which cyanocobolamin is linked to a diagnostic radionuclide. Collins does not disclose compounds in which cyanocobolamin is linked to boron-10. Schinazi discloses compounds containing boron-10

in which cyanocobolamin is linked to boron-10. Schinazi does not disclose that one of those compounds bearing B10 should be cyanocobolamin. However, it would have been obvious to one of ordinary skill to link B10 to cyanocobolamin to achieve the therapeutic benefits asserted by Schinazi.

In response, applicants have argued that the ordinarily skilled artisan would not have expected boron neutron capture therapy to be successful. However, Schinazi teaches otherwise.

Applicants have also pointed out that Schinazi discloses that, in treating urogenital cancers, the administered compound should be lipophilic; and since cyanocobalamin is itself hydrophilic, the artisan of ordinary skill would not expect success in the treatment of urogenital cancer. First, the instant claims encompass treatment of all forms of cancer, and in any tissue. Accordingly, what may be true for urogenital cancer may not be true for liver cancer; what may be true for liver cancer may not be true for brain cancer or lung cancer or melanoma. But in any case, applicants' argument is somewhat specious. To the extent that the hydrophil/lipophile argument is even relevant, the issue would be that of the lipophilicity of the **conjugate**, not the lipophilicity of the cyanocobalamin **prior** to attachment to the boron-containing lipophilic moiety. However, if applicants have evidence that conjugates of cyanocobalamin and (boron-containing) carborane are not effective to treat cancer, applicants may present evidence of the same, and the rejection will

certainly be reconsidered.

At the present time, however, the rejection is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

DAVID LUKTON, PH.D.
PRIMARY EXAMINER